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1

1 A Chemical Carrier

2

3 Technical Field

4

5 The invention relates to solid and fluid
6 formulations comprising an active agent and a
7 carrier for the active agent. This invention also
8 relates to the use of the carrier as a provider of
9 energy in drinks, foods and pharmaceutical
10 preparations.

11

12 Background Art

13

14 Starches are comprised of α -glucans (amylose and
15 amylopectin in variable proportions, amounting to
16 ~82 to 89%), moisture (~11 to 17%), lipids (cereal
17 starches only, <1.5%) and protein (~0.5%) with some
18 α -glucan phosphate-esters (especially in potato
19 amylopectin). Plants produce starches in different
20 sizes and shapes which reflect the botanical origin.
21 In rice starch for example, the granules are <5 μ m in
22 diameter while in potato starch they may exceed
23 50 μ m. The amylose fraction of starches comprise
24 predominantly linear α -(1-4)-glucan molecules with a
25 molecular weight of ~0.25 to 0.50 million Daltons.
26 Amylopectin molecules are much larger with a

1 molecular weight of a few million Daltons (probably
2 8-10 million Daltons) and comprise a heavily
3 branched structure of small unit chains (~15 to 80
4 glucose units long). The unit chains are like
5 amylose α -(1-4)-glucans (~95% of bonds) but are
6 linked together by α -(1-6) bonds (~5%). Native
7 starch granules contain double helices of
8 amylopectin which associate together to form
9 crystalline laminates which are interspersed with
10 amorphous amylopectin branch regions and amylose
11 chains.

12

13 The properties of native starches from different
14 botanical origins may be modified by genetic,
15 chemical, enzymatic and/or physical processing.
16 During the last few centuries, novel mutations have
17 been developed where the ratio of amylose to
18 amylopectin in the starches has been modified to
19 create 'high amylose' starches where the α -glucan
20 fraction may represent >70% amylose (<30%
21 amylopectin) and 'waxy' starches where the
22 amylopectin fraction may represent >70% amylopectin
23 (<30% amylose). Modern methods of 'transgenic'
24 technology may also be used to create novel glucans
25 within starch granules with different chain lengths,
26 distributions and potentially even sugar residues
27 other than glucose. Chemical methods have been used
28 to enhance the properties of starch granules where
29 residues may be added by chemical bonding,
30 stabilisation may be achieved by cross-linking or
31 molecular weight may be reduced by hydrolysis (with
32 for example acids). Glucose syrups may be made from

1 starches by acid hydrolysis but are more often made
2 by enzymatic hydrolysis (below). Here, amylases
3 (specifically α -amylase) and amyloglucosidase can be
4 used to produce syrups with variable proportions of
5 α -dextrins, different chain lengths and sugars
6 (glucose and maltose). Physically, starches may be
7 pre-gelatinised (heated in water to remove
8 crystallinity and dried to make 'instant' products)
9 or damaged (e.g. milled to remove ordered structure)
10 to moderate their functionality also.

11

12 Dextrins represent hydrolytic products of starches.
13 They are produced using a number of approaches as
14 discussed above.

15

16 Extensive acid hydrolysis may be used to produce low
17 molecular weight dextrins (<degree of
18 polymerisation, DP, ~20) where they may be branched
19 or linear, together with sugars in variable
20 proportions. The extent of hydrolysis is described
21 relative to the amount of reducing power compared to
22 a standard dextrose solution (dextrose equivalence,
23 DE). When glucose syrups are purchased they are
24 defined in terms of DE which suit specific
25 applications. These products are used extensively
26 in the food industry in confectionery, desserts,
27 drinks, cakes and pastries etc. where there is a
28 requirement for sweetness and product 'body'. In
29 the pharmaceutical industry there is a similar need
30 for glucose syrups in for examples pastilles and
31 tinctures with a need for pure glucose (dextrose) in
32 for example intra-venous products.

1 Less extensive acid hydrolysis of starches (with
2 some transglucosidation and repolymerisation) is
3 achieved by treating dry starches with acids and
4 heating at high temperatures. These dextrin
5 products are described as 'pyrodextrins' which
6 readily disintegrate in water and progressively
7 solubilise. They are classified as 'white',
8 'yellow' or 'British Gums'. These dextrins have
9 varying disintegrating and solubilising
10 characteristics and have specific applications as
11 for example tablet excipients.

12

13 Cyclodextrins are ring forms of dextrin oligomers.
14 The rings may contain six, seven or eight glucose
15 residues forming a hydrophobic core and hydrophilic
16 exterior. Hydrophobic residues (e.g. drugs) may be
17 located inside these cores and provide a vehicle for
18 drug delivery. A number of manufacturers prepare
19 cyclodextrins and their industrial utilisation is
20 quite well established (below).

21

22 Unlike the pyrodextrins, α -(limit)-dextrins
23 generated by α -amylase hydrolysis are not employed
24 as high molecular weight products (where there is
25 limited hydrolysis), either in the food or
26 pharmaceutical sectors. Similarly, β -limit dextrins
27 produced by hydrolysis of soluble starches
28 (generating the dextrins from amylopectin and
29 maltose sequentially from the α -glucan non-reducing
30 ends discussed below) are not used extensively in
31 these industries. The α -limit dextrins become more

1 soluble as hydrolysis is extended which, although
2 random, is initially restricted to starch amorphous
3 regions. The β -limit dextrans are highly soluble as
4 exterior chains of amylopectin have been hydrolysed
5 (to maltose) leaving short stubs attached to the
6 (high molecular weight) branched limit-dextrin
7 residues. β -limit dextrans are not at present
8 commercially available in significant quantities.

9

10 According to the National Starch web directory
11 (<http://www.foodstarch.com/directory>), a dextrin may
12 be defined as:

13

14 'Dextrans are starch hydrolysis products obtained in
15 a dry roasting process either using starch alone or
16 with trace levels of acid catalyst. The products
17 are characterised by good solubility in water to
18 give stable viscosities. Four types exist: White,
19 Yellow, British Gums and Solution-stable dextrans.'

20

21 Note that in reference to this commercially accepted
22 term, citations in patents referring to the use of
23 'dextrans' (e.g. Gregory (1983) and Gole et al
24 (1994), as discussed below) exclude β -limit dextrans
25 since they can only be produced in the solubilised
26 and not the dry state.

27

28 The properties of different dextrans are, as
29 discussed above, very different in terms of their
30 chemical and physical properties. They also have
31 different properties with respect to their potential

1 to be hydrolysed by different enzymes. Comparisons
2 are broadly made as follows:

3

4 Comparison of properties of different dextrans

5

6 Note that commercial 'dextrans are produced by
7 heating starches in the presence of a very small
8 amount of acid which induces hydrolysis,
9 transglucosidation and repolymerisation.

Dextrin	Product characteristics	Chemical properties	Physical properties
β -limit dextrin [Not a dextrin according to common commercial/ industrial usage of the term, see definition above]	White powder produced by hydrolysing solubilised amylopectin (from starch) with β -amylase	Molecular weight of dextrin ~ 50% that of amylopectin. Incorporates no amylose residues. Maltose would be present (from amylose and amylopectin hydrolysis) unless removed by for example dialysis or chromatography.	Soluble powder with no granular or crystalline form - i.e. amorphous.
British	Dextrin,	Hydrolysed	Dark

Gums [True commercial dextrin]	usually yellow or brown and darker than standard 'yellow dextrins' below. Powder form produced by roasting ~ dry starch at high temperatures at ~ neutral pH.	starches incorporating residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	coloured and relatively soluble - especially when heated - in water.
Maltodextrin [Not a dextrin according to common commercial/ industrial usage of the term, see definition above]	Produced from extensive acid or α -amylase (α -limit dextrin) hydrolysis of starch. Component of glucose syrups.	Branched dextrins comprising α -(1-4) and α -(1-6) bonds. Low molecular weight (degree of polymerisation, DP, < ~ 20) soluble branched product.	Soluble dextrins with reducing power much greater than starch polysaccharides but less than free sugars. Dextrose equivalence (DE), 5-20.
White Gums [True commercial]	Dextrin, usually ~ white. Powder	Hydrolysed starches incorporating	Light coloured and relatively

dextrin]	form produced by roasting ~ dry starch at relatively low temperatures at low pH.	residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	soluble - especially when heated - in water.
Yellow Gums (also referred to as Canary Gums) [True commercial dextrin]	Dextrin, yellow. Powder form produced by roasting ~ dry starch at relatively high temperatures at low pH.	Highly converted hydrolysed starches incorporating residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	Yellow coloured and relatively soluble - especially when heated - in water.

- 1 Cyclodextrins and their derivatives have been used
- 2 extensively in pharmaceutical applications and
- 3 details may be found in a number of patent sources
- 4 (e.g. Uekama et al, 1989).

1
2 As discussed above, amylopectin can be converted to
3 β -limit dextrin by conversion with β -amylase. This
4 enzyme works from the non-reducing end of the
5 amylopectin molecule hydrolysing the exterior
6 (external) chains leaving stubs (G2-G3) attached to
7 the β -limit dextrin. Typically, 50-60% of the
8 amylopectin is hydrolysed in this way (converted to
9 maltose) reducing the molecular weight accordingly
10 (from for example ~8 million Daltons to ~3 million).
11 These products are readily hydrolysed by α -amylase
12 and especially amyloglucosidase to glucose. The
13 amylopectin molecule is sparingly soluble and slowly
14 retrogrades (crystallises) from solution. The β -
15 limit dextrin, is however, highly soluble and would
16 not readily retrograde from solution.

17
18 One important application of solid dose formulations
19 is the application in rapid release oral dose
20 (buccal melt) type formulations. These products
21 have been described by Ohno et al (1999) in relation
22 to their buccal type formulations and those of their
23 competitors. The proposed advantage of the Ohno et
24 al (1999) technology over their competitors is the
25 capacity to make solid formulations that might
26 disintegrate rapidly. The technology describes the
27 use of a pharmaceutically active agent, erythritol,
28 crystalline cellulose and a disintegrant.

29
30 Fast dissolving formulations have been described by
31 Makino et al (1993) where they describe the use of
32 an active ingredient, a carbohydrate and a barely

1 sufficient amount of water to moisten the surface of
2 particles of the said carbohydrate into a tablet
3 form and a fast dissolving tablet obtained by this
4 method. The carbohydrate fraction is defined as to
5 include sugar, starch-sugars, lactose, honey, sugar
6 alcohols and tetroses with tablets which are porous
7 with excellent digestibility, solubility and
8 adequate strength. It is stated that the
9 carbohydrate to be employed must be 'soluble in
10 water and does not adversely affect the active
11 ingredient (for example, decomposition of the active
12 ingredient)'. The disclosure concentrates on sugars
13 as they would be expected to dissolve and disperse
14 apart from the active ingredients in tablets without
15 entrapment-type interactions upon hydration. The
16 disclosed preference is to use 'sucrose, glucose,
17 maltitol, xylitol, erythritol and so on' [sugar and
18 sugar alcohols but no mention of oligo- or
19 polysaccharides]. Also mentioned are 'sugar,
20 starch-sugars, lactose, honey, sugar-alcohols,
21 tetroses, sucrose, coupling-sugars,
22 fructooligosaccharides, palatinose and so on'.
23 Sugars are elaborated as 'glucose, maltose, powdered
24 syrup, starch syrup, isomerised sugar (fructose) and
25 so on'. For lactose they elaborate as 'lactose,
26 isomerised lactose (lactulose), reduced lactose
27 (lactitol)'. For sugar alcohols they include
28 sorbitol, mannitol, reduced malt syrup (maltitol),
29 reduced starch saccharides, xylitol, reduced
30 palatinose and so on'. Tetroses are defined as
31 obtained from glucose fermentation.
32

1 Zydis is a technology platform owned by R P Scherer
2 (now Cardinal Health) where fast dissolving
3 formulations are manufactured by blending and
4 dissolving an active ingredient with a polymer,
5 sugar and other ingredients followed by freeze
6 drying (lyophilisation or in the context of the
7 patent description 'sublimation'). Although some
8 authors have proposed that freeze dried formulations
9 are problematic and have proposed solvent
10 extractable matrices or matrices incorporating
11 solvent sublimation to add advantage (Gregory et al,
12 1983; Gole et al, 1994) the Zydis technology is
13 still popular. Gregory et al (1983) and Gole et al
14 (1994) discuss the use of dextrans in their
15 (sublimed/freeze dried) delivery matrices but do not
16 define which type of dextrin which is very confusing
17 in view of the very different chemistries and
18 physical properties of different dextrans. The
19 authors do not have interests in tablet production
20 (by compression) per se. In reality, only some
21 dextrans would impart desirable characteristics
22 (forming the appropriate structure and melt type
23 characteristics) in these freeze dried matrix types
24 whilst others would be detrimental. For example,
25 the dextrans present in maltose syrups have a very
26 low molecular weight and would be very different
27 (size, shape, structure, solubility, reducing power,
28 rheology, digestibility etc.) from dextrans produced
29 from very limited (acid or α -amylase) hydrolysis of
30 native starches. In fact, the only example Gregory
31 (1983) cite is 'dextrin' (not type, source etc.)
32 while the Gole et al (1994) application is based on

1 (exemplified by) maltodextrin (which is generated by
2 α -amylase but not β -amylase as previously
3 discussed). It is apparent in these patents that
4 the applicants do not understand the breadth of
5 different chemical species and properties in
6 different types of dextrans. Different dextrans
7 have different properties and chemistries.

8

9 Brief Description of the Invention

10

11 According to the invention, there is provided a
12 formulation, typically a pharmaceutical formulation,
13 comprising an active agent and at least one
14 excipient, wherein the at least one excipient
15 comprises a β -limit dextrin.

16

17 Typically, the formulation is suitable for
18 administration to the human or animal body.

19

20 In this specification, the terms "pharmaceutical
21 product" and "pharmaceutical formulation" should be
22 understood to include therapeutic and prophylactic
23 pharmaceutical products as well as health promoting
24 or nutritional products which include vitamins,
25 minerals, herbal remedies, proteins, amino acids and
26 the like and consumable products such as breath
27 fresheners. The product could be used as a
28 nutritional or pharmaceutical agent and may be
29 administered on (e.g. topical on skin) or within the
30 body by one or more route (e.g. oral, nasal,
31 vaginal, pulmonary, rectal, intravenous,
32 intramuscular, intraperitoneal, etc.) for its

1 specific activity. As such, the term "active agent"
2 should not be construed as being limited to
3 pharmaceutically active agents, but may comprise
4 cellular material (e.g. cells, microorganisms),
5 genes, nutritional supplements and flavours or
6 fragrances or the like.

7

8 In one embodiment, the active agent is a
9 pharmaceutically active agent.

10

11 In a preferred embodiment, the β -limit dextrin is a
12 carrier for the active agent.

13

14 Typically, the pharmaceutical formulation is a
15 bioadhesive pharmaceutical formulation in which the
16 β -limit dextrin carrier acts as a mucoadhesive
17 excipient. In this specification, the term
18 "bioadhesive pharmaceutical formulation" should be
19 understood to mean pharmaceutical formulations which
20 are intended to deliver an active agent to a mucosal
21 membrane of a mammalian body. In humans, such
22 mucosal membranes include those located in the
23 buccal cavity, intestine, the nasal cavity, the
24 lungs and throat, the vagina, and the rectum

25

26 In one embodiment, the bioadhesive pharmaceutical
27 formulation is a buccal-melt type product, or a
28 wafer. In another embodiment, the bioadhesive
29 pharmaceutical formulation is a powder for use in
30 aerosol delivery formulations, typically aerosol
31 formulations for nasal or pulmonary delivery. The
32 material may be solubilised/dispersed and

1 administered accordingly (for example in the mouth
2 as a solution or the nasal/pulmonary route as a
3 spray/mist (or equivalence)).

4

5 In an alternative embodiment, the bioadhesive
6 pharmaceutical formulation is a thin film, typically
7 of the type commonly used as a carrier of breath
8 freshener fragrances.

9

10 The invention also relates to the use of β -limit
11 dextrin as a mucoadhesive carrier. In particular,
12 the invention relates to the use of β -limit dextrin.
13 as a mucoadhesive carrier in a pharmaceutical
14 formulation. The invention also relates to the use
15 of β -limit dextrin as a mucoadhesive carrier in non-
16 pharmaceutical applications such as, for example, a
17 thin-film breath freshener.

18

19 In one embodiment which is a formulation for oral
20 delivery, the pharmaceutical formulation of the
21 invention is a buccal melt product. Typically, the
22 pharmaceutical formulation is in a form selected
23 from the group comprising: particulate; capsule;
24 tablet; freeze dried matrix; wafer; and liquid. In
25 this specification, the term "particulate product"
26 should be understood to include powders, granules,
27 flakes and the like. Typically, the particulate
28 product is derived from pulverised freeze dried
29 matrices, granulated, roller dried, or spray dried
30 material. Suitably the particulate product is a
31 pharmaceutical product. In one embodiment of the

1 invention, the particulate product is an inhalation-
2 type product.

3

4 The invention also relates to a liquid formulation
5 comprising an active agent, and a dispersant,
6 wherein the dispersant comprises β -limit dextrin.
7 Typically, the liquid formulation is a
8 pharmaceutical formulation.

9

10 The invention also relates to the use of β -limit
11 dextrin as an excipient in a pharmaceutical
12 formulation.

13

14 The invention also relates to a nutritional product
15 comprising β -limit dextrin. Suitably, the β -limit
16 dextrin is used as an energy source. Typically, the
17 β -limit dextrin is a main energy source in the
18 product. This is not always the case, however, as it
19 may be consumed in conjunction with other
20 carbohydrates (or energy sources). In one
21 embodiment, the nutritional product is an energy
22 drink of the type sold under the Trade Name
23 "Lucozade". In an alternative embodiment of the
24 invention, the nutritional product is a
25 confectionary product, such as, for example, a sweet
26 or a chocolate product.

27

28 The invention also relates to the use of β -limit
29 dextrin as an energy source in a clinical-
30 nutritional product. In particular, the invention
31 relates to the use of β -limit dextrin as an energy
32 source in an energy drink.

1
2 In one embodiment, the β -limit dextrin is obtainable
3 by hydrolysing starch with β -amylase.

4 This invention also relates to the use of β -limit
5 dextrin alone as a source of energy. It may be
6 formulated in drinks, foods, feeds and the like for
7 this purpose.

8
9 The invention also relates to the use of β -limit
10 dextrin as a dispersant in liquid pharmaceutical and
11 non-pharmaceutical formulations.

12
13 The invention also relates to the formation of β -
14 limit dextrin *in situ* in the formulated product
15 where the substrate (amylose or amylopectin) is
16 hydrolysed within the finished or near-finished
17 product by the (added or endogenous) β -amylase.

18
19 Melt Formulations

20
21 These are rapidly disintegrating formulations which
22 are intended to be dissolved very rapidly in the
23 buccal cavity (mouth). Generally these formulations
24 lack physical strength. One example of the use of
25 the β -limit dextrans in buccal melt type products is
26 presented in Example 1.

27
28 Use of β -limit dextrans in freeze dried matrices and
29 tablet (including melt) type formulations

30

1 These have not been defined elsewhere. As discussed
2 above, freeze dried matrices have been described
3 (containing 'dextrins') but do not incorporate the
4 use of β -limit dextrins. Furthermore, tablet
5 formulations with melt or fast/slow/controlled
6 release type formulations have not been described at
7 all where β -limit dextrins have been incorporated.
8 The unique characteristics of β -limit dextrins in
9 freeze dried matrices and tablets are unexpected and
10 surprisingly. Examples of the use of freeze dried
11 matrices is presented in Example 2 and 3.

12

13 Powder formulations incorporating β -limit dextrins

14 These molecules can be formed from dried matrices
15 (e.g. from pulverised freeze dried matrices or from
16 granulated or spray dried material). We have found
17 that active agents can be incorporated into these
18 matrices before drying or blended together
19 subsequently. These applications are discussed
20 below. This material clearly has applications in
21 tablets (above), sachets etc. and as an inhalation
22 type (nasal/pulmonary) carrier as the material is
23 quite 'sticky' when hydrated.

24

25 Liquid formulations incorporating β -limit dextrins

26

27 This dextrin is highly soluble. Also, because of
28 the removal of exterior chains (of amylopectin) the
29 product cannot retrograde (recrystallise) easily if
30 at all from solution. This makes the product very

1 stable in solution and appropriate as a dispersing
2 component in liquid pharmaceutical (and non-
3 pharmaceutical) preparations. The solutions readily
4 form mists when sprayed making ideal carriers for
5 pulmonary and nasal delivery.

6

7 Film formulations incorporating β -limit dextrans

8

9 A dextrin solution incorporating active agents (as
10 described above) forms thin film when oven dried.
11 This makes it a suitable carrier in food, personal
12 care or pharmaceutical preparations.

13

14 Brief Description of the Figures

15

16 The invention will be more clearly understood from
17 the following description of some embodiment
18 thereof, given by way of example only, with
19 reference to the accompanying Figures in which:

20

21 Fig. 1 is a graph showing the rheological properties
22 of glucose (bottom line) and β -limit dextrin (top
23 line) solutions containing 1% theophylline;

24

25 Fig. 2 is a graph comparing the mucoadhesive forces
26 (N) of tablets containing β -limit dextrin and
27 Carbopol;

28

29 Fig. 3 is a graph comparing the mucoadhesive forces
30 (N) of tablets containing Chitosan, Carbopol, and a
31 placebo;

32

1 Fig. 4 is a graph comparing the mucoadhesive forces
2 (N) of a mixture of β -limit dextrin and sodium
3 alginate, and sodium alginate alone; and

4

5 Figs. 5 and 6 are graphs showing the dissolution
6 properties of formulations according to the
7 invention.

8

9

10 Detailed Description of the Invention

11

12 β -limit Dextrin Production

13

14 These dextrans may be produced from starches of
15 different botanical origins and different genetic
16 modifications, chemical, enzymatic or physical
17 derivatives. Since all the amylose is converted to
18 maltose, it is much more cost effective to use high
19 amylopectin ('waxy type') starches where there is a
20 higher proportion of amylopectin - the origin of the
21 β -limit dextrin.

22

23 The dextrin may be produced by a number of routes
24 and the following method does not exclude material
25 produced by other routes nor using other sources of
26 enzyme or processing conditions.

27

28 The dextrin is produced in conjunction with maltose
29 from the α -glucan hydrolysis. In the method
30 described below, the maltose is removed by dialysis
31 leaving pure dextrin. However, the maltose could be

1 left in the product as an option (to impart
2 sweetness and novel functionality).

3

4 Waxy maize starches (c. 25g) were dissolved in 500ml
5 acetate buffer (0.02M, pH 4.8) at 100°C for at least
6 1 hour. After cooling to room temperature,
7 crystalline sweet potato β -amylase (5×10^3 units,
8 Sigma A-7005) was added and the mixture was
9 thoroughly mixed. The mixture were then transferred
10 into dialysis tubing (Visking code DTV 12000.13.000)
11 and incubated for 36 hours at 37°C under dialysis
12 against the same buffer, which was renewed three
13 times during the first 3 hours and twice afterwards.
14 Chromatography would be a preferred industrial
15 separation method. After the reaction had been
16 terminated by heating the mixture for 10 mins at
17 100°C, the coagulated protein was removed by
18 centrifugation, and then ethanol was added to the
19 solution. The resulting precipitate was collected by
20 centrifugation, dissolved in water (250ml) and then
21 re-precipitated by the addition of ethanol. The
22 precipitate recovered on centrifugation was finally
23 dissolved in water and then dried (below).

24

25 Drying Tests (dextrin alone)

26

27 The dextrin was dried using freeze drying and spray
28 drying (including use of small pilot scale Büchi
29 mini spray dryer model B-191). The spray dried
30 material is a fine powder with good flow
31 characteristics. The freeze dried material makes a
32 fine lyophilised matrix. This may be milled to a

1 powder which tends to be a little electrostatic in
2 character. The material was also wet granulated
3 from the dried materials which was, itself, readily
4 tableted (below).

5

6 Dextrin Characterisation

7

8 Composition

9

10 Moisture content: depends on drying protocol (<9%)

11 Protein: <0.5%

12 Ash: <0.3%

13 Molecular weight: $3.1 \times 10^6 \text{ g mol}^{-1}$

14

15 Solubility

Solvent/Temperature (°C)	Solubility (w/v, %)
Water 25°C	31
Water 50°C	34
0.01M HCl (pH2) 25°C	33
0.01M HCl (pH2) 50°C	43
0.01M NaOH (pH12) 25°C	34
0.01M NaOH (pH12) 50°C	36

16 Stability (5% solution, 25°C)

17

18 The stability was assessed where the time for the
19 solution to become opaque then form precipitates at
20 different pH's was determined.

pH	Storage stability (days)
----	--------------------------

3	94
7	9
11	17

1 Molecular characterisation

2 The product of β -amylase hydrolysis was analysed by
3 gel permeation chromatography (GPC, using Sepharose
4 CL-2B gels) according to Karkalas and Tester (1992)
5 before and after dialysis (to remove maltose).
6 Accordingly the retention time and molecular weight
7 of the dextrin was smaller than the native
8 amylopectin (with maltose present prior to
9 dialysis). This confirms that the native amylopectin
10 molecules were selectively hydrolysed.

11

12 Rheological Properties

13

14 To prove that the rheological properties of a drug
15 in solution with a sugar (glucose) or the β -limit
16 dextrin are different in terms of interactions the
17 following experiment was conducted.

18

19 Samples of theophylline and either glucose or the β -
20 limit dextrin were dispersed in water (to give a
21 concentration of 1% theophylline, w/w and either 1%
22 with respect to glucose or beta-limit dextrin, w/w)
23 within sealed screw capped tubes. These were sealed
24 and mixed and kept in a 25°C water bath. The

1 viscosity was immediately determined using a
2 Brookfield DV-III Viscometer (Brookfield Engineering
3 Laboratories, INC., USA) fitted with a cone and
4 spindle CP-40 system (2.4cm dimension and 0.8°
5 angle) with a thermostatically controlled
6 temperature of 25°C. A silicon viscosity standard
7 (96.2mPas at 25°C) from Brookfield was used for
8 calibration. The results are shown in Figure 1.

9

10 Enzyme digest with or without dialysis to remove
11 maltose.

12

13 The properties of formulations containing the
14 dextrin which have none, some or all of the maltose
15 removed (howsoever) differ in their properties.
16 These are also considered below.

17

18 Energy Product

19

20 The solubility of the dextrin and its high molecular
21 weight make it very valuable as a component of
22 drinks to provide a slow release of energy.

23 Applications

24

25 Examples

26

27 1. Melting Formulations

28

29 β -limit dextrin was wet-granulated as described
30 later in this application. Two formulations were
31 prepared where the Carbopol formulation was used as

1 a standard as it has well established mucoadhesive
2 properties.

3

4 Formulation:

5 20% β -limit dextrin

6 6% PVP 44000

7 1% Magnesium stearate

8 73% Spray-dried lactose

9

10 Formulation:

11 20% Carbopol 934

12 6% PVP 44000

13 1% Magnesium stearate

14 73% Spray-dried lactose

15

16 Tablets were made using a single-punch tablet press
17 (Manesty F3, Liverpool, UK) and 6 mm diameter flat
18 punches. β -limit dextrin formulation produced
19 thicker tablets due to the lower bulk density of the
20 mixture. The tablet's crushing strength was measured
21 using a tablet hardness tester (Model TBH28, Erweka,
22 Heusenstamm, Germany). At compaction pressure of
23 35N, crushing strength of 45N was obtained for β -
24 limit dextrin formulation whereas the value for
25 Carbopol formulation was 160N.

26

27 Mucoadhesion test was carried out in vitro using
28 double strength nutrient agar coated with a 5%
29 solution of porcine mucin over the surface.
30 Measurements were made with a Texture Analyser (TA-
31 XT2i, Stable Micro Systems, Surrey, UK) by applying

1 a force of 0.15N and a contact time of 10 minutes.
2 The adhesive forces obtained are shown in Figure 2.

3

4 As can be seen in Figure 2, the mucoadhesive force
5 of the Carbopol formulation was about 0.40N on
6 average, with the average value for the β -limit
7 dextrin formulation about the same (0.38N). Under
8 these conditions therefore the mucoadhesive force of
9 β -limit dextrin was very similar to the Carbopol.

10

11 The contact force was then increased to 0.25N. The
12 proportion of β -limit dextrin was increased to 30%
13 and this was found to be the optimal concentration.
14 Three formulations were prepared as follow:

15

16 Formulation:

17 30% β -limit dextrin
18 6% PVP 44000
19 1% Magnesium stearate
20 63% Spray-dried lactose

21

22 Formulation:

23 30% Carbopol 934
24 6% PVP 44000
25 1% Magnesium stearate
26 63% Spray-dried lactose

27

28 Formulation:

29 30% Chitosan
30 6% PVP 44000
31 1% Magnesium stearate
32 63% Spray-dried lactose

1
2 A 'placebo' tablet was also prepared that contained
3 no known mucoadhesion. Mucoadhesion force was
4 measured as mentioned above with contact time of 10
5 minutes. The average mucoadhesive forces are 0.097N,
6 0.245N and 0.450N for tablets containing placebo,
7 chitosan and Carbopol respectively comparing to the
8 value of 0.464N for β -limit dextrin.

9
10 The results (see Figure 3) demonstrate that the β -
11 limit dextrin does have significant mucoadhesive
12 properties.

13
14 The mucoadhesive property of β -limit dextrin can be
15 improved by addition of other polysaccharides (e.g.
16 sodium alginate). Two formulations were prepared as
17 follow:

Ingredients (mg/tablet)	A	B
β -limit dextrin	20	-
Sodium alginate	10	30
PVP 44 000	6	6
Magnesium stearate	1	1
Spray-dried lactose	63	63

18 The mucoadhesive forces measured as described above
19 are 0.629N and 0.544N for formulation A and
20 formulation B respectively, although 0.464N was
21 obtained without addition of sodium alginate for the

1 previous formulation (Page 24). The above results
2 (see also Figure 4) show that the addition of
3 alginate does increase the mucoadhesive force of β -
4 limit dextrin significantly.

5

6 2. Dried matrices

7

8 Solutions/suspensions containing the dextrin and
9 theophylline (e.g. 10% with respect to the dextrin
10 and 0.1% with respect to theophylline) were freeze-
11 dried where easily hydratable matrices were formed.
12 These melt type formulations can also be milled to
13 produce fine powders.

14

15 The matrices 'melted' or rather dissolved and
16 dispersed exceedingly easily when water came into
17 contact with them. It is evident that freeze-dried
18 products could be made from this material.

19

20 3. Tablet Formulations

21

22 It was found that the dextrin could be tableted
23 directly to form products with different drugs. The
24 following examples exemplify this.

25

26 a. Direct compression

27

28 β -limit dextrin was prepared from waxy maize starch
29 and was spray dried to form a fine powder.

30

31 b. Granulation

32

1 Samples (15g) of the β -limit dextrin (dried by
2 freeze drying) was wet massed with 5ml water using
3 an FP296 mixer (Kenwood Ltd, UK). Granules were then
4 spread evenly over a drying tray and dried overnight
5 at 60°C. Dried granules were passed through a 300 μ m
6 mesh to produce a free-flowing powder.

7

8 Two formulations were produced using the same water-
9 soluble drug but different types of additional
10 tableting excipient since the tablet release matrix
11 (first) formulation was not easily tabletable with
12 drug alone (as friable tablets were produced). Each
13 formulation was then tested using a standard USP II
14 paddle dissolution apparatus (ST-7 model, Caleva
15 Ltd, UK) at 37°C in 1000ml water (λ_{max} propranolol-HCl
16 = 298nm).

17

18 Formulation 1. β -limit dextrin, hydrophilic
19 excipient and tablet release formulation

20

21 Formulation:

22 40% β -limit dextrin

23 20% Microcrystalline cellulose (Avicel 101)

24 20% Lactose

25 20% Propranolol-HCl

26

27 The formulation was mixed for 30 minutes using an
28 orbital Turbula™ mixer (Glen-Creston Ltd, Middlesex,
29 UK). The resultant mixture was then tableted with a
30 7.95mm concave punch and die set using an E2 single
31 punch tablet press (BWI-Manesty Ltd, Liverpool, UK).

1 Tablet properties made according to hydrophilic
2 tablet.

3

4 Formulation

	Weight	Thickness	Hardness	Diameter
No.	(mg)	(mm)	(N)	(mm)
1	194.9	3.99	36	7.95
2	201.6	4.09	40	7.94
3	181.6	3.79	28	7.93
4	201.0	4.06	46	7.93
5	179.6	3.75	25	7.93
6	190.7	3.95	32	7.96
7	177.9	3.73	32	7.94
8	194.3	4.00	24	7.94
Mean	190.2	3.92	33	7.94
SD	± 9.4	± 0.14	± 7	0.01

5 The dissolution properties of the tablets are shown
6 in Figure 5.

7

8 Formulation 2. β -limit dextrin, hydrophobic
9 excipient and tablet release formulation

10

11 Formulation:

12 50% β -limit dextrin

13 25% Emcompress® (Dibasic calcium phosphate)

14 25% Propranolol·HCl

15

1 The components were mixed and compressed as with the
2 previous formulation (1).

3

4 Tablet properties made according to hydrophobic
5 tablet formulation

No.	Weight (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)
1	205.0	3.91	<10	7.94
2	192.9	3.72	<10	7.94
3	197.4	3.85	<10	7.94
4	199.2	3.78	<10	7.94
5	199.9	3.76	<10	7.96
6	194.0	3.74	<10	7.94
7	193.7	3.65	<10	7.96
8	197.4	3.83	<10	7.97
Mean	197.4	3.78	<10	7.94
SD	± 4.0	± 0.08		0.01

6 The dissolution properties of the tablets are shown
7 in Figure 6.

8

9 Better weight uniformity is obtained indicative of
10 improved powder flow. Low hardness may be improved
11 by adding a compression binding agent.

12

13 4. Powder Formulations

14 These may be made from milling dried matrices (e.g.
15 '2'). However, powders can also be made directly by
16 for example spray drying.

1
2 Solutions containing the dextrin and theophylline
3 (e.g. 10% with respect to the dextrin and 0.1% with
4 respect to theophylline) were spray dried where very
5 fine powders were prepared that disperse very easily
6 upon hydration. These may be tableted (see above) or
7 utilised in sachet type formulations. It is
8 anticipated that pulmonary type delivery products
9 could be made from small particles comparable or
10 smaller than dimensions present in these powders.

11

12 5. Liquid Formulations

13

14 The β -limit dextrin was dissolved in water (for
15 example a 10% solution) with theophylline (for
16 example 0.1%). The solution was found to be very
17 stable at room temperature and could be used as a
18 liquid formulation for oral delivery of drugs and
19 for parenteral administration.

20

21 Liquid formulations were also made with the dextrin
22 alone. It is clear that the stability of the dextrin
23 makes it valuable as a provider of energy in
24 appropriate nutritional products. The material will
25 have a slower hydrolysis profile with for example α -
26 amylase compared to maltodextrin because of its
27 higher molecular weight. Spray mists were made with
28 the solutions using a variety of devices and support
29 the application in nasal/pulmonary applications.

30

31 6. Film formulation

32

1 β -Limit dextrin was dissolved in deionised water, to
2 which vitamin A solution (1mg/ml) was added to give
3 final concentration of 1% for β -Limit dextrin. Film
4 was obtained after convection-oven drying the
5 mixture in a foil tray at 30, 40 or 50°C overnight.

6

7 7. Enhancement of drug solubility

8

9 It was noted that rather surprisingly the β -limit
10 dextrin could facilitate the dissolution of drugs.
11 There are many potential applications with respect
12 to dispersing and solubilising insoluble compounds.
13 The following example indicates that this is so.

14

15 Drug interaction and stability with β -limit dextrin 16 in solution

17

Drugs (1%)	Water	β -limit dextrin (5%)	β -limit dextrin (10%)
Ascorbic acid	Dissolved	Dissolved	Dissolved
Glucose	Dissolved	Dissolved	Dissolved
Theophylline	Not suspended	Suspended	Suspended
Aspirin	Not suspended	Suspended	Suspended

18

19

20 8. Dialysis

21

22 It is also apparent that the material could be
23 potentially used for intra-peritoneal dialysis if a
24 low osmotic α -glucan is required. The product would
25 potentially fulfil the need in this area provided by
26 oligosaccharide type products like 'icodextrin'

1 produced by ML Laboratories. The following example
2 indicates that this is so.

3

4 The osmolality of β -limit dextrin solution (5%) was
5 measured using an advanced 3300 cryoscopic osmometer
6 which was pre-calibrated with 0.9% aqueous sodium
7 chloride solution. Maltodextrin (Maldex 150BB,
8 Amylum) was used to act as a control. The results
9 are presented as follow.

10

11 The COP_{10K} (the measured osmotic pressure of the
12 solution across a membrane with a pore size of
13 10,000 Daltons) of the same sample solutions was
14 also measured using an Osmomat 030 colloid osmotic
15 pressure osmometer. A 6% haes solution was used to
16 calibrate the pore size as it varies depending on
17 the age of the membrane. The COP_{10K} results are given
18 as follow.

19

Samples(5%)	Osmolality (Milliosmol/kg)	COP10K (mmHg)
β -limit dextrin	16.2	3.9
Maltodextrin	43.7	20.9

20 9. Adhesions

21

22 Similarly to the icodextrin product discussed above,
23 it is anticipated that the material could function
24 to prevent tissue adhesion.

25

26 10. Drink Formulations

1 Drinks were prepared from 0-20% β -limit dextrin and
2 flavourings (<0.1%). The product is not sweet.
3 Hence, sweetening was added in (a) the form of sugar
4 (sucrose, 5-10%) or (b) aspartame (<0.1%) plus
5 flavours. The products had a much better
6 organoleptic property and could be used as the basis
7 of formulated energy products.

8

9 The invention is not limited to the embodiments
10 hereinbefore described which may be varied in detail
11 without departing from the spirit of the invention.

12

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